REMARKS

Claims 20 and 37 have been amended solely for greater clarity. Support for the amendments can be found throughout the specification. No new matter has been introduced. Applicants further submit that the amendments are made merely to expedite allowance of claims directed to most commercially relevant embodiments of the present invention. Applicants reserve the right to pursue claims of similar or differing scope in the future.

Applicants note that the Examiner has withdrawn the previous claim rejections under 35 USC 102(b), 103(a), and 112, second paragraph. However, the Examiner cites new prior art in this Office Action.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election/Restriction

Applicants note with appreciation that the Examiner has rejoined independent claims 20 and 37 as well as their dependent claims in view of Applicants' pervasive arguments.

Information Disclosure Statement

The Examiner asserts that the references cited on pages 15 and 16 of the specification have not been incorporated into an Information Disclosure Statement (IDS). The Examiner acknowledges that "[t]he information disclosure statements filed 2/2/03 and filed 2/22/05 have been considered as to the merits before First Action." Office Action, page 2, lines 19-20.

Applicants point out that Applicants actually filed an IDS on September 2, 2003, rather than February 2, 2003. The Examiner has considered and initialed the IDS filed on September 2, 2003 (a copy is enclosed herewith as **Exhibit A**). Applicants note that the IDS filed on September 2, 2003 includes most of the prior art listed on pages 15 and 16 of the specification. Some of the references listed on pages 15 to 16 are not included in the IDS since they relate to the documents discussed in the background and are not material to the present application. Thus, the previously filed IDSs suffice to fulfill Applicant's duty of disclosure.

The Examiner is respectfully requested to reconsider and withdraw this objection.

Claim Objections

The Examiner objects to claims 20 and 37 due to the use of the acronyms ALTE and SIDS. Applicants have amended these two claims to include the definitions of these abbreviations, thereby obviating the objection.

Rejections of Claims 20, 22, 24, 27, 33, and 39 under 35 USC 102(b)

The Examiner has rejected claims 20, 22, 24, 27, 33, and 39 under 35 USC 102(b) as being allegedly anticipated by Stoltenberg et al. (Pediatric Research, 1992, 31(4):372-375). Applicants respectfully traverse this rejection.

Specifically, the Examiner indicates that Stoltenberg et al. teach the measurement of immunoglobulin responses in SIDS and ALTE in infants. The Examiner notes that the reference discloses "that SIDS increases incidents with respiratory tract infections and it is speculated that the immune response in the respiratory track might be one possible 'trigger mechanism' in SIDS (assessor of susceptibility to development of SIDS)." The Examiner further indicates that "IgA was elevated in both SIDS samples and infants with infections (infectious control) when compared with controls (predetermined standard). IgA was more elevated in infectious samples when compared with SIDS samples. IgA was elevated more so than the other immunoglobulins (IgM and IgG)." See Office Action, page 4, the first paragraph.

Applicants respectfully submit Stoltenberg et al. fail to anticipate the present invention. The presently claimed invention is directed to a method of assessing potential susceptibility to development of ALTE and/or SIDS in a subject including: (a) determination of the IgA level in a sample from the subject; and (b) prediction of susceptibility to development of ALTE and/or SIDS by comparison of said IgA level with a predetermined standard.

By contrast, Stoltenberg et al. are completely silent as to assessment of susceptibility to development of ALTE or SIDS and fail to provide any insight as to how an assessment of susceptibility to development of ALTE or SIDS might be carried out. Indeed, the data in Stoltenberg et al. relate to post-mortem studies. There is not a single piece of data relating to live children; nor is there any indication as to how the risk of development of ALTE or SIDS (in live children) might be assessed. As such, Applicants respectfully submit that it is inappropriate to cite this reference on the grounds of lack of novelty against the instant claims to a method of

assessing susceptibility to ALTE and/or SIDS since the claims are inherently directed to live children. Further, the cited reference clearly fails to disclose any test for susceptibility to ALTE and/or SIDS and provides no direction to a skilled artisan as to how IgA or any other immunoglobulin might be used in such a test.

The Examiner points to page 372 of Stoltenberg et al. in which it is indicated that "an immune response in the respiratory tract might be one possible 'trigger mechanism'" in SIDS (assessor of susceptibility to development of SIDS)" (Office Action, page 4, lines 1-3, emphasis added). It appears to be the Examiner's position that a "trigger mechanism" equates to an "assessor of susceptibility or development of SIDS." Applicants respectfully disagree.

By using the term "might," Stoltenberg et al. are clearly speculating as to the "trigger mechanism." Applicants submit that the Examiner's interpretation of the term "trigger mechanism" is an entirely unwarranted and unsubstantiated extrapolation of the author's comment. Stoltenberg's speculation about an immune system response being a trigger for SIDS provides no indication that the immune response, and in particular a specific component of the immune response, would be a useful predictor of SIDS or ALTE. It certainly does not constitute a disclosure that IgA, one of the myriad components of the immune response, would be useful as a predictor of SIDS or ALTE. Further, Stoltenberg et al. simply fail to teach or suggest how to use IgA as a predictor.

Applicants remind the Examiner that MPEP 2112 clearly points out that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic."

Applicants point out that Stoltenberg's data or teachings do not expressly or inherently anticipate the present invention for the reasons that follow.

First, as the samples of Stoltenberg et al. were taken from dead children, there was no way of knowing at what point the immune response that might have acted as a trigger was induced and, hence, at what time it might have been usefully measured prior to death.

Second, tissue specimens Stoltenberg et al. were obtained from two different sites – the tracheal wall and the duodenal mucosa. As indicated on page 373, first column, last paragraph, the tracheal lamina propria and submucosa of SIDS victims contained significantly more IgM

plasma cells than controls, but no difference was found for IgA and IgG. Accordingly, even if the data in the Stoltenberg et al were indicative of an immunological state that mirrored that at a time sufficiently in advance of death that it could be monitored, a "normal" child and a child who was about to die of SIDS would present with similar IgA in the tracheal lamina propria and submucosa. So there would be no predictive value in assessing IgA to determine the child's susceptibility to development of ALTE/SIDS. Applicant emphasize that nothing in the Stoltenberg's data were indicative of an immunological state that mirrored that at a time sufficiently in advance of death that it could be monitored.

Third, even if the data in the Stoltenberg et als were indicative of an immunological state that mirrored that at a time sufficiently in advance of death that it could be monitored, in both the tracheal wall and the duodenal mucosa, the number of IgA plasma cells was less than in the infectious controls. As such, a child with an infection would present with more IgA than a child who was about to die of SIDS. Again, it is clear that this provides no predictive value in assessing IgA to determine the child's susceptibility to development of ALTE/SIDS.

Fourth, Stoltenberg et al. indicate that the duodenal mucosa of children who died from SIDS contained more IgA plasma cells than the "normal" children (the non-infectious group). However, even if the data in the Stoltenberg et al were indicative of an immunological state that mirrored that at a time sufficiently in advance of death that it could be monitored (and Applicant says that there is nothing in the data provided by Stoltenberg et al that would lead the reader to think that this was the case), it is entirely impractical to perform duodenal biopsies as a routine screening test for identifying infants at risk of ALTE/SIDS.

In view of the above, Applicants respectfully submit that Stoltenberg et al. fail to meet the limitations of the present claims and thus fail to anticipate the claimed subject matter in independent claim 20 or 39. For the same reasons, all claims depending from claim 20 or 39 are novel over Stoltenberg et al. Reconsideration and withdrawal of this rejection are requested.

Rejections of Claims 23, 29-32, and 38 under 35 USC 103(a)

Claims 23 and 29 (dependent on claim 20) are rejected as being unpatentable over Stoltenberg et al. in view of Gleeson et al. (Pediatric Research, 193, Vol 33, no.6, pages 554-556). Claims 30-32 (dependent on claim 20) are rejected as being unpatentable over Stoltenberg et al. in view of Rylatt et al. (WO 97/09620). Claim 38 (dependent on claim 20) is rejected as

being unpatentable over Stoltenberg et al. in view of Foster et al. (US Patent No. 4,444,879). Applicants respectfully traverse these rejections.

Specifically, the Examiner states that Stoltenberg et al. differ from the instant invention in not specifically teaching sample collections up to 2 weeks after an upper respiratory tract infection (URTI) or radial immunodiffusion techniques (Office Action, page 5, lines 6-8). The Examiner alleges that one of ordinary skill would have been motivated to measure IgA levels at an increased expression (after URTI) "because the prior art has shown that IgA expression in infants is low or nonexistent." See Office Action, page 6, lines 7-9.

First, Applicants have argued above that Stoltenberg et al. do not teach all the elements of the claimed invention, including, but not limited to, use of IgA as a predictor of ALTE and/or SIDS as recited in independent claim 20. None of the other cited art (Gleeson et al., Rylatt et al.) bridges the gap between Stoltenberg et al. and the claimed invention. Thus, the cited art, singly or in combination, fails to teach or suggest all the claim limitations.

Moreover, Stoltenberg et al. do not provide any extrapolation from the results of their experiments in dead children to a predictive method to be applied in live children. In fact, Stoltenberg et al. suggest that the next most appropriate investigation in gaining an understanding of the "trigger mechanism" for SIDS is "more studies involving measurements of various cytokines in cerebrospinal fluid and brain tissue from SIDS cases and controls as well as animal experiments" (see last paragraph of Stoltenberg et al.; emphasis added). Stoltenberg et al. do not even mention or hint the sort of prospective study of the immunoglobulin IgA in saliva of live children such as that carried out by the present inventors, which was required to ultimately result in the presently claimed invention. Accordingly, there would be no motivation for one of ordinary skill to combine the teaching of Stoltenberg et al. with any of the other cited references in order to achieve the presently claimed invention. Thus, Applicants submit that the rejection is rendered moot.

Combination of Stoltenberg et al. with Gleeson et al.

The Examiner asserts that claims 23 and 29 are obvious in light of the teaching of Stoltenberg et al. and Gleeson et al. The Examiner indicates that Stoltenberg et al. do not teach sample collections up to 2 weeks after a URTI, but asserts that Gleeson et al. teach "a method of

measuring SIDS [Applicants assume that the Examiner means IgA here] after URTI in an infant." Office Action, page 5, lines 6-12.

Applicants point out that Stoltenberg et al. are deficient in many more ways beyond simply the lack of teaching of a sample collection up to 2 weeks after a URTI. In fact, Stoltenberg et al. do not teach or recommend the measurement of any component of the immune response in making an assessment of the susceptibility of a child to ALTE/SIDS and, insofar as it suggests any further investigations, all suggestions are limited to studies either in dead subjects (SIDS victims) or animals. As such, there is no teaching in Stoltenberg et al. of any measurement of IgA or any other immune response component in a live child. Accordingly, there is no motivation for the skilled artisan to combine the teachings of Stoltenberg et al. with that of Gleeson et al. in which the IgM, IgG and IgA status of live children is assessed.

Moreover, with respect to claim 23, even if the teachings of the two citations were combined, Gleeson et al. would not motivate the skilled person to take a sample 2 weeks after a URTI to measure IgA levels with a view to determining susceptibility to SIDS. The data in Gleeson et al. clearly show that a mild respiratory tract infection was diagnosed at 3.5 weeks of age in the SIDS victim (page 554, second column, second paragraph). It is clear from the graph at Figure 1 that two weeks after the URTI, the child's IgA levels were well within the 90th percentile (in fact, about half that of those at the highest end of the 90th percentile). As such, Gleeson et al. teach away from the measurement of IgA 2 weeks after a URTI as a means of determining susceptibility to SIDS.

With regard to claim 29, the combination of a disclosure of radial immunodiffusion techniques with Stoltenberg et al. does not provide the presently claimed invention. As indicated above, Stoltenberg et al. do not teach or suggest a method for determining susceptibility to development of ALTE/SIDS by measuring IgA or indeed any other immune response component and, as such, a teaching of radial immunodiffusion for measurement of IgA does not render the invention of claim 29 obvious.

Combination of Stoltenberg et al. with Rylatt et al. or Foster et al.

Claims 30-32 are rejected as being unpatentable over Stoltenberg et al. in view of Rylatt et al. (WO 97/09620). Claim 38 is rejected as being unpatentable over Stoltenberg et al. in view

of Foster et al. (US Patent No. 4,444,879). See Office Action, pages 6-8. Applicants respectfully disagree.

Applicants have argued above that Stoltenberg et al. do not teach or suggest a method for determining susceptibility to development of ALTE/SIDS by measuring IgA or any other component of the immune response. Neither Rylatt et al. nor Foster et al. can bridge the gap between Stoltenberg et al. and the claimed invention. Since independent claim 20 is patentably non-obvious over Stoltenberg et al., all claims depending from claim 20 recite further limitations thereon (e.g., claims 30-32 and 38), and hence are a fortiori patentably non-obvious over Stoltenberg et al.

Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 103(a).

Rejections of Claims 21-34 and 36-38 under 35 USC 103(a)

Claims 21-22, 24-28, 33-34, and 36-37 are rejected as being unpatentable over Stoltenberg et al. in view of Friedman et al. (Clinical and Experimental Immunology, 1996, 103(2):206-211). Claims 23 and 29 (dependent on claim 21) are rejected as being unpatentable over Stoltenberg et al. in view of Friedman et al. and further in view of Gleeson et al. Claims 30-32 (dependent on claim 21) are rejected as being unpatentable over Stoltenberg et al. in view of Friedman et al. and further in view of Rylatt et al. Claim 38 (dependent on claim 21) is rejected as being unpatentable over Stoltenberg et al. in view of Friedman et al. and further in view of Froster et al. Applicants respectfully disagree.

Combination of Stoltenberg et al. with Friedman et al.

Stoltenberg et al. do not teach or suggest a method which involves measuring IgA1 in any sample, let alone a sample from a live child. Applicants have argued above that Stoltenberg et al. do not teach or suggest how to use IgA or IgA1 as a predictor for susceptibility to development of ALTE/SIDS.

Friedman et al. disclose a study of infants immunized against rotavirus. While certainly some infants die of rotavirus, Friedman et al. are not directed in any way to the teaching of methods of assessing potential susceptibility to ALTE and/or SIDS. In fact, Friedman et al. are concerned with measurement of a normal response to infection with rotavirus, i.e., elevated

levels of IgA subclasses such as IgA1 and IgA2. In contrast, the present application is concerned with detecting IgA and IgA1 such that in cases in which there is an abnormal response to infection in terms of the level of the immunoglobulin, a prediction of the susceptibility of developing ALTE and/or SIDS can be made. In addition, Friedman et al. provide no indication that IgA1 can be used as a predictor of ALTE and/or SIDS. Indeed, Friedman et al. are completely silent on assessment of potential susceptibility to development of ALTE and/or SIDS.

Thus, even if the teachings of Stoltenberg et al. and Friedman et al. were combined, the combination still fails to teach the limitations of the present claims. Furthermore, absent any indication in the cited prior art that IgA1 could be used as a predictor of ALTE and/or SIDS, one of skill in the art would not have been motivated to combine Stoltenberg et al. with Friedman et al. in order to achieve the presently claimed invention. Thus, Applicants submit that the rejection is rendered moot.

Combination of Stoltenberg et al. and Friedman et al. with Gleeson et al.

The Examiner alleges that claims 23 and 29 are obvious in light of Stoltenberg et al. combined with Friedman et al. and Gleeson et al. The examiner indicates that Stoltenberg et al. combined with Friedman et al. differs from the invention of claims 23 and 29 in that it does not teach sample collections after a URTI or radial immunodiffusion techniques. The Examiner considers the data in Figure 1 of Gleeson et al. and indicates that the increase in IgA was five times higher than the age-related median for 8 week-old infants.

Applicants point out to that claim 23 defines a method according to claim 20 or 21 wherein the sample is taken "at the time of, or any time up to approximately 2 weeks after," a URTI. As indicated above, the SIDS victim was diagnosed with a URTI at 3.5 weeks. According to Figure 1 in Gleeson et al., the child's IgA level at 4 weeks was only slightly above the age-related median and, indeed at 5.5 weeks (if one assume that the increase from 4 to 6 weeks was steady) as indicated above, the SIDS child's IgA levels was well within the 90^{th} percentile and about half that of those at the highest end of the 90^{th} percentile. As such, Gleeson et al. provide no motivation for the skilled person to measure IgA, or IgA1 levels, at the time of, or any time up to approximately 2 weeks after a URTI as is claimed in claim 23. In fact, Gleeson et al. teach away from the presently claimed invention for the reasons indicated.

Combination of Stoltenberg et al. and Friedman et al. with Rylatt et al. or Foster et al.

The Examiner alleges that claims 30-32 and 38 respectively are unpatentable over Stoltenberg et al. and Friedman et al combined with Rylatt et al. and Foster et al., respectively.

Applicants have argued above that the combination of Stoltenberg et al. and Friedman et al. does not teach or suggest a method for determining susceptibility to development of ALTE/SIDS by measuring IgA or IgA1. Neither Rylatt et al. nor Foster et al. can bridge the gap between the propose combination (of Stoltenberg et al. and Friedman et al.) and the claimed invention. Since independent claim 21 is patentably non-obvious over Stoltenberg et al. and Friedman et al., all claims depending from claim 21 recite further limitations thereon (e.g., claims 30-32 and 38), and hence are a fortiori patentably non-obvious over the cited references.

Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 103(a).

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. If an additional fee is due, please charge our **Deposit Account No. 18-1945, under Order No. BSWV-P01-002.**

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Respectfully submitted,

By _____

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